UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,108	12/20/2001	Timothy David Osslund	01017/38834F	7916

7590 10/17/2006

Marshall Gerstein & Borun LLP
6300 Sears Tower
233 South Wacker Drive
Chicago, IL 60606

EXAMINER	
LUCAS, ZACHARIAH	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 10/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/032,108	OSSLUND, TIMOTHY DAVID	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62, 66, 75, 76, 79, 81-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62,66,75,76 and 81-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 62, 66, 75, 76, 79, and 81-83 are pending and under consideration.

2. The Art Unit location of your application, and the examiner to whom the case has been docketed in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Zachariah Lucas in Art Unit 1648.

3. In the prior action, mailed on January 24, 2006, claims 62, 66, 75, 76, 79, and 81-83 were pending and rejected. In the amendment of July 27, 2006, the Applicant amended claims 62, 66,75, 76, 79, and 81.

4. Because this action raises new grounds of rejection not necessitated by amendment, the action is made Non-Final.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. **(Prior Rejection-Withdrawn)** In the prior action, claims 62, 66, 75, 76, 79, and 81-83 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. In view of the amendments to the claims, the rejections are withdrawn.

7. **(New Rejection)** Claims 62, 66, and 81-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention. These claims are drawn to modified G-CSF molecules comprising a substitution in "an external loop." The claims are rejected because it is not clear what residues form the referenced external loops.

On page 25 of the application, the helices of the G-CSF protein are identified as follows: the A helix is amino acids 11-39, the B helix is amino acids 72-91, the C helix is amino acids 100-123, and the D helix is amino acids 143-173. This page also refers to a pair of smaller helices between residues 45 and 53. Page 68 further identifies the AB helix as being residues 58-72 of the protein.

However, it is noted that the application provides conflicting information as to the residues that form the loops between these sequences. For example, on page 25 of the application, residues 100-123 and 143-173 are respectively identified as forming the C and D helices of the protein. However, on page 68 of the application, the CD loop is described as comprising residues 119-145. Additionally, page 68 also indicates that residues 100-118 are found "between the B and C helices," which conflicts to the prior identification of residues 100-118 as falling wholly within the C helix. In addition, while the disclosure of page 68 indicates that the AB helix is formed by residues 58-72, the disclosure of Figure 4 indicates that residue 47 falls within the AB helix.

These conflicting teachings raise uncertainty as to what residues the Applicant considers to fall within which regions of the protein. For example, is unclear how residues 119-123 and 143-145 can be both part of the indicated helices and of the indicated loops, or as to what residues form the AB helix. Moreover, as there is no identification of the residues that form the other loops of the protein, and in view of the conflicting information provided above, it appears

that the Applicant has a different means for identifying the residues forming the loops than merely those that are not part of the helices identified on page 25. As the application does not clearly identify the residues that the Applicant considered to form the various regions, especially the external loops, and for the reasons indicated above, the indicated claims are rejected as indefinite.

Claim Rejections - 35 USC § 102 and 103

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. **(Prior Rejection- Maintained/Restated in part)** Claims 62, 66, 75, 76, and 79 were rejected under 35 U.S.C. 102(b) as being anticipated by Shaw et al., U.S. 4,904,584. These claims are directed to modified forms of the C-CSF protein.

Each of these claims requires that the modified G-CSF comprises a substitution of another amino acid for the lysines found in positions 17 and 41 (or 16 and 40 where the N-terminal methionine is not included in the sequence) of the G-CSF sequence of SEQ ID NO: 2.

Claim 62 additionally requires that the modified G-CSF comprises an alteration such that at least one lysine residue is inserted into an external loop of the protein as described in Figure 4 of the application, and wherein the inserted lysine is modified with a PEG molecule.

Claim 66 further requires that the modified G-CSF, as described in claim 62, further includes a substitution of an amino acid not essential for structural integrity within the sequences of at least one of the A, C, or D helices (other than the substitution of the A helix lysine at position 17.

Claim 75 reads on modified G-CSF proteins comprising the substitutions at positions 17 and 41, and at least one additional substitution of an amino acid not essential for structural integrity within the sequences of C or D. Claims 76 and 79 read on embodiments wherein, respectively, the additional substitutions are in at least 2 of helices A, C, and D, or in each of helices A, C, and D. Each of these claims ha also been amended to require that at least one residues is modified with PEG.

The Applicant asserts that the Shaw reference does not teach a G-CSF variant comprising a modification in the external loops of the protein, other than the modification of the lysine at position 41. This argument is found persuasive. The rejection is therefore withdrawn from claims 62 and 66. Moreover, it is noted that Shaw also does not teach embodiments wherein the G-CSF protein is modified in each of the A, C, and D helices. The rejection of claim 79 is therefore also withdrawn.

With respect to claims 75 and 76, and to previously non-rejected claims 81-83, the rejection is restated as a rejection of claims 75, 76, and 81-83 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Shaw. This restatement is explained below.

The Applicant traverses the prior anticipation rejection of claims 75 and 76 on the basis that the claims require that the G-CSF mutants have modifications other than in the A helix, and that Shaw does not teach such modifications. This argument is not found persuasive.

Claims 75 and 76 read as indicated above. The claims permit the substitutions to be in the C or D helices, alone or in combination with a substitution in helix A. Shaw teaches embodiments comprising the substitutions at positions 17 and 41 (positions 16 and 41 in the Shaw reference), and comprising additional substitutions at (a) positions 24, 35, 147, and 148 (corresponding to positions 23, 34, 146 and 147 in the Shaw reference), (b) positions 24, 35, and 167 (166 in Shaw), (c) positions 24, 35, and 170 (169 in Shaw), and (d) positions 24, 35, 167, and 170. Each of these embodiments is disclosed the Table provided in columns 13-14 of the patent, which is more easily read on page 23 of the corresponding PCT publication, WO 89/05824 (of record in the IDS of December 2001). The substitutions at each of positions 16, 24, 35, and 41 are, as asserted by the Applicant, within helix A. However, the substitutions at positions 147, 148, 167, and 170 fall within the D helix. Moreover, none of these positions are identified as residues essential for structural integrity in the present application. See, page 66. The reference therefore teaches mutations meeting the first two structural requirements (subparts (a) and (b)) of the indicated claims.

Moreover, it is also noted that each of these variants includes the modification K41R. Nissen et al. (U.S. 6,555,660- of record in the June 2003 IDS) teaches that G-CSF variants having this substitution show reduced in vitro activity relative to the native G-CSF. See e.g., column 58. In view of these teachings, the variants disclosed by the Shaw reference would inherently also show such reduced activity, and therefore also meet the limitations of claims 81 and 83.

With respect to the claim limitations of subpart (b) of claims 75 and 76 (and the function of claim 82), requiring the modification of at least one lysine with a PEG (thus resulting in a protein with extended in vivo half-life), it is noted that the Shaw reference teaches that the indicated mutants have been modified in at least one of the positions with "a modification in accordance with this invention, e.g., PEGylation, at each reactive lysine residue." Column 14, lines 48-56. These teachings either indicate that the disclosed mutants have been modified such that, or render obvious the modification of, the indicated lysines with a PEG molecule (thereby necessitating the 102/103 rejection as restated above). The reference teaches that such PEGylation of the proteins results in the maintenance of a desirable circulatory level of the protein (i.e., an increase in the in vivo serum half-life). Col 1, lines 15-27. Similar such teachings are also found in the Nissen reference. Nissen, see e.g., abstract, and column 2. Because the Shaw reference either teaches, or renders obvious, the mutant G-CSF molecules having the sequence modifications of claims 75 and 76 wherein the mutants are PEGylated, the reference also inherently meets the functional limitation of claim 82.

For the reasons above, the anticipation rejection is either maintained over claims 75 and 76, and extended to claims 81 and 83; or is restated as a rejection of these claims under 35 U.S.C. 103(a) over the teachings of the Shaw reference.

11. **(New Rejection)** Claims 62, 66, and 81-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shaw, and further in view of Bazan et al., Immunology Today 11: 350-54. As was indicated above, claim 62 reads on a modified G-CSF comprising substitutions of the lysines at positions 17 and 41, and an alteration such that at least one lysine residue is inserted into an external loop of the G-CSF protein as described in Figure 4 of the application, and wherein the inserted lysine is modified with a PEG molecule. Claim 66 reads on such modified G-CSF proteins, further comprising at least one amino acid substitution at least one of the A, C, or D helices.

Shaw has been described previously and above. As previously described, this reference teaches the modification of proteins, including G-CSF, such that certain lysines native to the sequence are substituted with another sequence, including the lysines of positions 17 and 41, and embodiments wherein the proteins further comprising modifications to at least one of the A or D helices. However, the reference does not specifically teach or suggest modified forms of G-CSF wherein the protein has been modified to include a lysine in an external loop such that a PEG molecule may be attached thereto.

It is noted that the teachings of Shaw do indicate that those of ordinary skill in the art were aware of potential problems with the insertion of the lysines into active regions of the protein (e.g. regions required for protein structure or activity). This can be seen from the

teachings of column 4 of the reference, indicating that certain activities of the protein may be abolished by insertion of the lysine into a region required for that activity. See also, Bowie et al., Science 247: 1306-10 (of record in the action mailed July 6, 2005). Thus, those of ordinary skill in the art would not, from the teachings of Shaw alone, have adequate suggestion or motivation to insert the lysines into a loop region of the G-CSF protein.

However, the teachings of Bazan indicate both that the generic structure of the G-CSF protein was known, and that the active regions of the protein are found in the helical domains. See e.g., page 352. In particular, Figure 2 of the reference shows general structures for G-CSF and related cytokines, including identification of helical and loop regions approximating those of the present application. Additionally, the text on page 352 indicates that G-CSF and homologous cytokines have their active regions (receptor binding regions) in the helical domains of the protein.

From these combined teachings, those of ordinary skill in the art would have been motivated to add lysines into the G-CSF molecule for PEG attachment in regions not required for protein structure or activity. The additional teachings of Bazan indicate that the loop regions of the protein would be appropriate regions for lysine insertion and PEG attachment as they were not expected to participate in the protein's activity. Thus, those of ordinary skill in the art would have had both motivation and a reasonable expectation of success in targeting the loop regions of G-CSF for lysine/PEG modification. The additional limitations of claim 75, relating to the helices would have been met as the Shaw reference teaches the examples of modified G-CSF proteins including substitutions, and particularly lysine→arginine substitutions in the A helix. It would have been obvious to those of ordinary skill in the art to use such modified G-CSF

molecules, or any of the other disclosed embodiments, as base molecules for additional modification in the loop regions. The combined teachings of these references therefore render the claims obvious.

12. **(New Rejection)** Claims 62, 66, 75, 76, 79, and 81-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Shaw, or Shaw in view of Bazan as applied, respectively, against claims 75, 76, and 81-83, or claims 62, 66, and 81-83 above, further in view of Bowie. The claims have been described above. As previously indicated, claim 79 varies from claim 75 and 76 in that the claim requires that there are addition modifications to the protein each of the A, C, and D helices. However, it is noted that the claim ascribes no function to such sequence modifications. Moreover, while the claim requires the PEGylation of a lysine in the protein sequence, there is no requirement as to where such a lysine may be found. The latter is also true with respect to claims 75 and 76.

The teachings of Shaw and of Shaw in view of Bazan have been described above. The Shaw reference teaches modified G-CSF proteins comprising the required substitutions for the native lysines at positions 17 and 41. The reference also teaches additional examples of G-CSF proteins modified to include additional lysines with PEG attached, including embodiments comprising mutations in the A, or the A and D helices. The additional teachings of Bazan also indicate that those in the art would have been motivated to insert lysines for PEG attachment outside of the loop regions.

However, as was indicated above, the application does not provide any purpose for the modification of the helix regions. As seen in the Bowie reference, those in the art would have

generally expected conservative mutations to be operable. Thus, it would have been obvious to those of ordinary skill in the art to use G-CSF mutants comprising conservative substitutions in the helix regions as functional equivalents for the native G-CSF.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Z. Lucas
Patent Examiner